American Journal of Gastroenterology

Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2004.04136.x

Relationship of Visceral Adipose Tissue to Recurrence of Adenomatous Polyps

David A. Sass, M.D., Robert E. Schoen, M.D., M.P.H., Joel L. Weissfeld, M.D., M.P.H., Lisa Weissfeld, Ph.D., F. Leland Thaete M.D., Lewis H. Kuller, M.D., Dr. P.H., Mary McAdams, M.S., Elaine Lanza, Ph.D., and Arthur Schatzkin, Ph.D.

Departments of Medicine; Epidemiology; Biostatistics; Radiology; and the University of Pittsburgh Cancer Institute; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Informational Management Services; Rockville, Maryland; and the National Cancer Institute, Bethesda, Maryland

OBJECTIVES: Insulin is a growth factor for colorectal cancer. Visceral adipose tissue (VAT) is strongly associated with insulin levels, and insulin and visceral obesity have been associated in cohort studies with colorectal cancer. The aim of this investigation was to determine whether VAT is associated with recurrence of adenomatous polyps, the precursor to colorectal cancer.

METHODS: As an ancillary study to the Polyp Prevention Trial, a randomized clinical trial that evaluated the effect of a low-fat, high-fiber, high vegetable and fruit diet on adenomatous polyp recurrence, subjects at one clinical center underwent measurement of VAT with a single-slice CT scan through the L4–L5 interspace. The scan was performed around the time of the subject's year 4 colonoscopy that determined adenoma recurrence.

RESULTS: Of 119 subjects, 44 of 84 men (52%) and 16 of 35 women (46%) had a recurrent adenoma ($p = 0.51$). Body mass index (BMI) and weight at baseline and at year 4 colonoscopy were unrelated to adenoma recurrence. In a multivariate model including visceral fat quartile, remote history of polyps, gender, age, and randomization group, only remote history of polyps was statistically significantly associated with recurrent adenoma with a relative risk of 4.6 (95% CI 1.7, 12.4, $p = 0.001$). There was no consistent monotonic trend of increased or decreased risk of recurrence as one ascended quartiles of adipose tissue for visceral, subcutaneous, or total abdominal fat.

CONCLUSION: In this study, no association between visceral adipose tissue and adenomatous polyp recurrence was observed. Further study and exploration of the role of VAT in adenoma progression is required.

INTRODUCTION

Colorectal cancer (CRC) is a significant public health problem and is the second leading cause of cancer-related mortality in the United States (1). Because treatment of advanced CRC is limited, prospects for CRC control must focus on early detection and prevention. Strong circumstantial evidence suggests that CRC develops from a precursor lesion, the adenomatous polyp (2).

Recurrence of adenomatous polyps in subjects with adenomas is common, about 10% of subjects have a recurrent adenoma per year (3). At the current surveillance intervals of 3–5 yr, about 30–50% of subjects have a recurrent adenoma. Little is known about the factors associated with recurrent adenomas. Endoscopic factors such as multiplicity and the presence of advanced adenomas have been associated with recurrent adenomas, though these factors are not consistently observed in all studies (3). Because surveillance of subjects with adenomas is one of the most costly aspects of screening (4), improvement in tailoring surveillance intervals is a priority.

Although there have been dramatic advances in understanding the genetic changes that accompany progression from adenomatous polyp to cancer, compelling evidence including migrant studies (5), and rapidly changing incidence and mortality (6) support a strong role of environmental factors in carcinogenesis. Obesity is one such factor. Many studies (5, 7, 8) have demonstrated a direct association between obesity, estimated by body mass index (BMI) and increased risk for CRC, especially in men. Recent epidemiologic data suggest that adipose tissue distribution, rather than overall adiposity, may be an important mediating factor in the association between BMI and CRC (9). Associations between waist circumference or waist-to-hip ratio, surrogate measures of intraabdominal fat or visceral adipose tissue (VAT), and subsequent development of CRC or large adenomas ($\geq$ 1 cm in size) have been demonstrated in cohort studies (9–11). Physical inactivity is another environmental factor

Supported by a grant from the National Cancer Institute (K07-CA72561) to RES.

and a third of the men had a remote history of adenomatous polyps (Table 1). The BMI [weight (kg)/height (meters^2)] was similar for men and women but men weighed more and were taller. The measurements of visceral fat, subcutaneous fat, and total fat are noted in Table 1. Men had more visceral fat ($p = 0.005$) but less subcutaneous fat ($p < 0.001$) and tended to have lower amounts of total fat ($p = 0.07$) (Table 1). As a percentage of total fat, men had more visceral fat than women (43.4% *vs* 29.3%, $p < 0.001$). Of 119 subjects, 44 of 84 men (52%) and 16 of 35 women (46%) had a recurrent adenoma ($p = 0.51$).

In Table 2 the relationship of the demographic variables, polyp history, and measures of obesity is examined in a univariate analysis to the recurrence of an adenoma at T4 colonoscopy. Gender, race, age, education, NSAID/ASA use, and smoking were unrelated to the recurrence of an adenoma (Table 2). A remote history of adenomas was highly associated with having a recurrent adenoma at T4 ($p = 0.0008$). Twenty-six of 35 (74.3%) of those patients with a prior adenoma had a recurrent adenoma compared with 34 of 84 (40.5%) of those without a previous adenoma. A family history of CRC was not associated with a recurrent adenoma. Those randomized to the intervention cohort had a 42.6% recurrence rate compared to 58.6% in the control group ($p = 0.08$). BMI and body weight at initiation into the trial (T0 time point) and at year four (T4 time point) were unrelated to adenoma recurrence (Table 2). There was also no relationship between weight change and recurrence of adenomas (T4–T0 time point). Similarly, there was no relationship between measures of total fat, visceral obesity, or subcutaneous fat and recurrence (Table 2).

Because of the differences in visceral and subcutaneous fat across gender (Table 1), men and women were divided into gender-specific quartiles for visceral, subcutaneous, and total fat. The ranges for the quartiles are provided in Table 3. Although in some quartiles there was a statistically significant reduction in recurrent adenoma in comparison to quartile 1, there was no consistent monotonic trend of increased or decreased risk of recurrence as one ascended quartiles of adipose tissue for visceral, subcutaneous, or total fat (Table 3). There was also no relationship between the relative percentage of visceral fat and recurrent adenoma.

In a multivariable model including visceral fat quartile, prior adenomas, gender, randomization group, and age, only prior adenomas were statistically significantly associated with an increased risk of adenoma recurrence with a relative risk of 4.6 (95% CI 1.7, 12.4, $p = 0.001$). In this small sample, randomization to the intervention group was protective, with a RR of 0.4 (95% CI 0.2, 0.9, $p = 0.03$), although in the trial as a whole the intervention had no effect on recurrence. Modeling adipose tissue measurements as a continuous variable did not affect the results. Models including aspirin use, NSAID use, family history, and smoking did not change the results and none of these variables were statistically significantly associated with recurrence of adenomas.

Table 2. Relationship of Subject Characteristics to Recurrent Adenoma at Year 4 Colonoscopy

	Recurrence N (%)	*P* Value
A. Demographic variables		
Gender		
Male	44/84 (52.4)	0.51
Female	16/35 (45.7)	
Race		
White	53/106 (50.0)	0.79
Non-white	7/13 (53.9)	
Education		
≤ High school	12/23 (52.2)	0.85
> High school	48/96 (50.0)	
Age (years ± SE)		
Recurrence (N = 60)	67.6 ± 1.21	0.20
No recurrence (N = 59)	65.4 ± 1.20	
NSAID use		
Yes	34/71 (47.9)	0.50
No	26/48 (54.2)	
ASA use		
Yes	27/53 (50.9)	0.92
No	33/66 (50.0)	
Ever smoking		
Yes	37/77 (48.1)	0.48
No	23/42 (54.8)	
B. Polyp history		
Prior adenomas		
Yes	26/35 (74.3)	0.0008
No	34/84 (40.5)	
Family history CRC		
Yes	16/33 (48.5)	0.79
No	44/86 (51.2)	
Randomization group		
Intervention	26/61 (42.6)	0.08
Control	34/58 (58.6)	
C. Anthropometric measures of obesity		
BMI at baseline (± SE)		
Recurrence	27.4 ± .51	0.83
No recurrence	27.3 ± .45	
Weight at baseline (kg ± SE)		
Recurrence	80.2 ± 1.8	0.93
No recurrence	80.0 ± 1.6	
BMI at year 4 (± SE)		
Recurrence	27.6 ± .60	0.72
No recurrence	27.3 ± .47	
Weight at year 4 (kg ± SE)		
Recurrence	80.7 ± 2.0	0.87
No recurrence	80.3 ± 1.8	
Weight difference (year 4 minus baseline ± SE)		
Recurrence	.52 ± .65	0.79
No recurrence	.30 ± .51	
D. CT measurements of obesity		
Total fat (± SE)		
Recurrence	461.50 ± 22.1	0.92
No recurrence	458.61 ± 17.6	
Visceral fat (± SE)		
Recurrence	186.8 ± 11.4	0.40
No recurrence	174.6 ± 9.0	
Subcutaneous fat (± SE)		
Recurrence	274.7 ± 13.9	0.63
No recurrence	284.0 ± 13.2	

Table 3. Relationship of Adipose Tissue Distribution to Recurrent Adenomas (Both Sexes Combined)

	Q1	Q2	Q3	Q4	*p*-Trend
Visceral fat (cm^3)					
Range					
Men	69.6–135.4	135.5–192.6	192.7–242.1	242.2–408.5	
Women	60.9–90.4	90.5–128.2	128.3–187.0	187.1–374.5	
No. of recurrences/no. of subjects	18/30	14/30	9/30	19/29	
Odds ratio (95% CI)	1.0	0.4 (0.1–1.3)	0.3 (0.1–0.9)	1.0 (0.3–3.3)	0.84
Subcutaneous fat (cm^3)					
Range					
Men	93.3–185.7	185.8–231.4	231.5–305.9	306–517.5	
Women	191.1–296.1	296.2–358.0	358.1–400.6	400.7–555	
No. of recurrences/no. of subjects	20/30	11/30	13/30	16/29	
Odds ratio (95% CI)	1.0	0.3 (0.1–1.1)	0.4 (0.1–1.3)	0.8 (0.2–2.6)	0.85
Total fat (cm^3)					
Range					
Men	165.3–331.0	331.1–434.6	434.7–550.7	550.8–863.9	
Women	263.9–423.2	423.3–486.3	486.4–548.1	548.2–862.7	
No. of recurrences/no. of subjects	20/30	10/30	12/30	18/29	
Odds ratio (95% CI)	1.0	0.3 (0.1–0.9)	0.3 (0.1–0.8)	0.9 (0.3–3.0)	0.87
% Visceral fat					
Range					
Men	25.1–38.7	38.8–43.7	43.8–47.5	47.6–63.9	
Women	13.2–22.1	22.2–27.9	28.0–36.9	37.0–52.4	
No. of recurrences/no. of subjects	19/30	11/29	10/31	20/29	
Odds ratio (95% CI)	1.0	0.3 (0.1–1.0)	0.3 (0.1–0.9)	1.0 (0.3–3.2)	0.97

Controlling for age, gender, remote prior adenomas, and randomization group.

Of 119 subjects, 10 had advanced adenoma recurrences at T4 colonoscopy. There was no association between advanced adenoma recurrence and VAT quartile.

DISCUSSION

This ancillary study to the Polyp Prevention Trial shows no convincing association between VAT or adipose tissue distribution and colorectal adenoma recurrence. Postulating an association is reasonable given the mounting evidence supporting the insulin hypothesis of CRC (9, 10, 18) the close association of VAT to insulin levels (19, 21, 22), and the demonstration of a biologic basis for a role for insulin in CRC (13, 15).

The traditional hypotheses for CRC pathogenesis including the bile acid hypothesis, and the effect of fiber on colonic transit and luminal carcinogen exposure are less appealing given the accumulating negative results from randomized trials and cohort studies against a pivotal role for fat (27), fiber (33–36), and micronutrients (27, 37). Furthermore, these traditional hypotheses do not explain well the association of abdominal obesity and insulin to CRC risk.

There are a number of limitations that must be acknowledged and accounted for in assessing the lack of an observed association between VAT and adenomatous polyp recurrence in this study. The primary limitation was that of a small sample size, which may have left the study underpowered to demonstrate a statistically significant association. Although our study never achieved the projected sample size based on the initial power calculation, the adenoma recurrence rate was 50% (significantly higher than anticipated) and, as such, our *post hoc* power analysis suggested adequate power to observe an effect. A larger sample, however, would permit a more accurate estimation of the true rate of recurrence in each of the quartiles of obesity.

We found a surprisingly high rate of recurrent adenomas in subjects in the lowest quartile of visceral and subcutaneous adiposity. This relatively high rate of recurrence in quartile 1 contributed to the absence of a significant trend in recurrence as one ascended quartiles of obesity. In addition, there was a greater proportion of subjects with adenoma recurrence in the lowest quartile BMI who participated in the study (47.4%) in comparison to the lowest quartile BMI without recurrence (34.9%) and in comparison to subjects with other, higher quartiles of BMI and adenoma recurrence (36.1%) or no recurrence (36.2%). This imbalance in participation may have skewed the results.

Another limitation is that CT measurement of VAT was performed at one time point, coincident with the year 4 colonoscopy, marking the endpoint of the PPT study. It is possible that rather than the absolute amount of VAT, it is the change in VAT over time that influences adenoma recurrence. A baseline VAT measurement at time zero would have helped to determine whether a change in VAT over time (4 yr) had an impact on the recurrence rate of adenomatous polyps. The argument against this postulated association,

however, is that no relationship was observed between weight change and recurrence in this sample, or in the trial as a whole (27).

Perhaps the intervention diet may have differentially affected VAT in the intervention cohort. In this study, because the recurrence rate for adenomatous polyps in the trial was similar between the intervention and control groups, the two groups were combined. However, if the intervention diet affected VAT, it could have obscured or altered the relationship between VAT and recurrent adenomas, and contributed to the lack of the observed effect in this study. While data suggest that there is a preferential reduction in VAT as opposed to subcutaneous adipose tissue in response to diet-induced weight loss (24, 38–41), there is no evidence that changing the content of the diet affects VAT. In the larger PPT trial, there was only a 0.65 kg weight loss in those randomized to the low-fat, high-fiber, high vegetable and fruit intervention diet, although this was statistically different from control subjects (42). That small amount of weight loss is unlikely to have a significant effect on the amount of measured VAT (24), so it is unlikely that VAT change was different in the intervention *versus* the control group. Finally, in this sample, there was no significant change in weight over time between those with recurrent adenomas compared to those without.

A further possibility for a null result is that our endpoint included all adenomas. In the Health Professionals Follow-up cohort study (9), waist circumference and waist-to-hip ratio, which are surrogate measures of VAT, were strong risk factors for the subsequent development of CRC and for large adenomas 1 cm in size or larger, which are considered at high risk for cancer development, but not with small adenomas that are less likely to progress (43). In our study we looked at the recurrence of all adenomatous polyps regardless of polyp size or histology. In the national PPT, only 6.3% of patients in the intervention arm and 7.0% in the control arm developed an advanced recurrent adenoma (defined as $\geq$ 1 cm in size, at least 25% villous elements, or with evidence of high-grade dysplasia). It is possible that VAT could affect the development of large or advanced adenomas; however, this study does not have adequate power to demonstrate such a relationship, given the small number of recurrent advanced adenomas. One also must be cautious about generalizing the findings in this sample as the results may have been different were data available for the trial as a whole. Finally, while VAT and its associated metabolic profile may be related to CRC, and development and perhaps recurrence of adenomas, the 3-yr period of observation in this small cohort may not have been enough of a time horizon to observe such an effect.

In conclusion, in this ancillary study to the PPT, no association between VAT and adenomatous polyp recurrence could be demonstrated. Future studies, using larger cohorts, followed for longer periods of time, and which include measurement of metabolic parameters such as insulin and insulin-like growth factors are anticipated to more fully evaluate the relationship between the insulin hypothesis and adenomatous polyp recurrence.

Reprint requests and correspondence: Robert E. Schoen M.D., M.P.H., Division of Gastroenterology and Hepatology, Mezzanine Level, C Wing, PUH, 200 Lothrop Street, Pittsburgh, PA 15213-2582.

Received February 24, 2003; accepted January 6, 2004.

REFERENCES

1. Ries LA, Wingo PA, Miller DS, et al. The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer 2000;88(10):2398–2424.
2. Bond JH. Polyp guideline: Diagnosis, treatment, and surveillance for patients with nonfamilial colorectal polyps. The Practice Parameters Committee of the American College of Gastroenterology [published erratum appears in Ann Intern Med 1994 Feb;15;120(4):347]. [Review] [90 refs]. Ann Intern Med 1993;119(8):836–43.
3. Schoen RE. Surveillance after positive and negative colonoscopy examinations: Issues, yields, and use. Am J Gastroenterol 2003;98(6):1237–46.
4. Marshall JR, Fay D, Lance P. Potential costs of flexible sigmoidoscopy-based colorectal cancer screening [see comments]. Gastroenterology 1996;111(n):1411–7.
5. Potter JD, Slattery ML, Bostick RM, et al. Colon cancer: A review of the epidemiology [review; 304 refs.]. Epidemiol Rev 1993;15(2):499–545.
6. Chu KC, Tarone RE, Chow WH, et al. Temporal patterns in colorectal cancer incidence, survival, and mortality from 1950 through 1990 [see comments]. J Natl Cancer Inst 1994;86(n):997–1006.
7. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women [see comments]. N Engl J Med 1995;333(11):677–85.
8. Will JC, Galuska DA, Vinicor F, et al. Colorectal cancer: Another complication of diabetes mellitus? Am J Epidemiol 1998;147(9):816–25.
9. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122(5):327–34.
10. Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91(13):1147–54.
11. Martinez ME, Giovannucci E, Spiegelman D, et al. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 1997;89(13):948–55.
12. Lee IM, Paffenbarger RS, Hsieh C. Physical activity and risk of developing colorectal cancer among college alumni. J Natl Cancer Inst 1991;83(18):1324–9.
13. Giovannucci E. Insulin and colon cancer [review; 219 refs.]. Cancer Causes Control 1995;6(2):164–79.
14. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: Are serum triglycerides and/or plasma glucose associated with risk? [review; 148 refs.]. Cancer Epidemiol Biomarkers Prev 1994;3(8):687–95.
15. Singh P, Rubin N. Insulin like growth factors and binding proteins in colon cancer [review; 190 refs.]. Gastroenterology 1993;105(4):1218–37.
16. Koohestani N, Tran TT, Lee W, et al. Insulin resistance and promotion of aberrant crypt foci in the colons of rats on a high-fat diet. Nutrition & Cancer 1997;29(1):69–76.
17. Tran TT, Medline A, Bruce WR. Insulin promotion of

colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996;5(12):1013–5.
18. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92(19):1592–1600.
19. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metabol 1982;54(2):254–60.
20. Schoen RE, Schragin J, Weissfeld JL, et al. Lack of association between adipose tissue distribution and IGF-1 and IGFBP-3 in men and women. Cancer Epidemiol Biomarkers Prev 2002;11(6):581–6.
21. Bjorntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 1990;10(4):493–6.
22. Krotkiewski M, Bjorntorp P, Sjostrom L, et al. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 1983;72(3):1150–62.
23. Ross R, Fortier L, Hudson R. Separate associations between visceral and subcutaneous adipose tissue distribution, insulin and glucose levels in obese women. Diabetes Care 1996;19(12):1404–11.
24. Ross R. Effects of diet- and exercise-induced weight loss on visceral adipose tissue in men and women [review; 36 refs.]. Sports Med 1997;24(1):55–64.
25. Schoen RE, Thaete FL, Sankey SS, et al. Sagittal diameter in comparison with single slice CT as a predictor of total visceral adipose tissue volume. Int J Obes Relat Metab Disord 1998;22(4):338–342.
26. Almendingen KH. Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up in situ for 3 yr? Am J Gastroenterol 2001;96(7):2238–46.
27. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group [see comments]. N Engl J Med 2000;342(16):1149–55.
28. Schatzkin A, Lanza E, Freedman LS, et al. The polyp prevention trial I: Rationale, design, recruitment, and baseline participant characteristics. Cancer Epidemiol Biomarkers Prev 1996;5(5):375–83.
29. Kvist H, Sjostrom L, Tylen U. Adipose tissue volume determinations in women by computed tomography: Technical considerations. Int J Obes 1986;10(1):53–67.
30. Borkan GA, Gerzof SG, Robbins AH, et al. Assessment of abdominal fat content by computed tomography. Am J Clin Nutr 1982;36(1):172–7.
31. Rossner S, Bo WJ, Hiltbrandt E, et al. Adipose tissue determinations in cadavers—A comparison between cross-sectional planimetry and computed tomography. Int J Obesity 1990;14(10):893–902.
32. Thaete FL, Colberg SR, Burke T, et al. Reproducibility of computed tomography measurement of visceral adipose tissue area. Int J Obes Relat Metab Disord 1995;19(7):464–467.
33. Alberts DS, Martinez ME, Roe DJ, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network [see comments]. N Engl J Med 2000;342(16):1156–62.
34. Fuchs CS, Giovannucci EL, Colditz GA, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women [see comments]. N Engl J Med 1999;340(3):169–76.
35. Terry P, Giovannucci E, Michels KB, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst 2001;93(7):525–33.
36. Bonithon-Kopp C, Kronborg O, Giacosa A, et al. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: A randomised intervention trial. European Cancer Prevention Organisation Study Group [see comments]. Lancet 2000;356(9238):1300–6.
37. Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group [see comments]. N Engl J Med 1994;331(3):141–7.
38. Ross R, Pedwell H, Rissanen J. Effects of energy restriction and exercise on skeletal muscle and adipose tissue in women as measured by magnetic resonance imaging. Am J Clin Nutr 1995;61(6):1179–85.
39. Stallone DD, Stunkard AJ, Wadden TA, et al. Weight loss and body fat distribution: A feasibility study using computed tomography. Int J Obes 1991;15(11):775–80.
40. Leenen R, van der KK, Deurenberg P, et al. Visceral fat accumulation in obese subjects: Relation to energy expenditure and response to weight loss. Am J Physiol 1992;263(5:Pt 1):t-9.
41. Chowdhury B, Kvist H, Andersson B, et al. CT-determined changes in adipose tissue distribution during a small weight reduction in obese males. Int J Obes Relat Metab Disord 1993;17(12):685–691.
42. Lanza E, Schatzkin A, Daston C, et al. Implementation of a 4-y, high-fiber, high-fruit-and-vegetable, low-fat dietary intervention: Results of dietary changes in the Polyp Prevention Trial. Am J Clin Nutr 2001;74(3):387–401.
43. Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas [see comments]. N Engl J Med 1992;326(10):658–62.